REMARKS

Claims 7-13, 21 and 30-33 are pending in the application. Claims 7, 21 and 30 were amended. Claim 10 was withdrawn from consideration as directed to a non-elected invention. Claims 8 and 33 were cancelled without prejudice to presentation in future, related applications. New claims 34 and 35 were added.

Claims 7, 21 and 30 were amended to further clarify the claimed invention and to recite specific cancer. New claims 34 and 35 were added, support for which can be found throughout the application as originally filed, including, for example, on page 14, lines 3-14.

No new matter was added.

Upon entry of this amendment, claims 7, 9-13, 21 and 30-35 will be pending.

Objections to the Specification

The Office has objected to the specification because it allegedly "contains embedded hyperlinks and/or other form of browser-executable code." Applicants have amended the specification to remove the embedded hyperlinks referenced to by the Office at paragraphs [0279], [0312], [0360], [0401], [0459], [0469], [0473], [0509], [0595], [0603], [0720], [0769] and [0776] of the published application.

Request for Information

Pursuant to 37 C.F.R. §1.105, the Office requires the Applicant and assignee to provide certain information "that the examiner has determined is reasonably necessary to the examination of this application." Specifically, the Office queries:

> (1) What is the name of the gene product comprising SEQ ID NO:23702 as used in publicly available databases (e.g. p53, pten, ras, vegft)?
>
> (2) What probes on an Affymetrix array (e.g. the HG-U133 array)hybridize to SEQ ID NO:23702?

(Office Action, page 5). The Office points out that where "the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item."

Applicants attempted to obtain the information requested by the Office and set forth the following:

> (1) Applicants note that SEQ ID NO:23702 corresponds to a 101 bp exon for BCAP31 on chromosome X. The sequences flanking the exon correspond to the intronic regions and include a 182 bp repeat element.
>
> (2) Applicants are not aware of any probes on publicly available Affymetrix arrays which hybridize to SEQ ID NO:23702.

In view of the foregoing remarks, Applicants submit that the information provided herewith is fully responsive to the Examiner's Requirement for Information.

Rejections under 35 U.S.C. §112, first paragraph (enablement)

Claims 7-9, 11-13, 21 and 30-33 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office alleges that the specification does not disclose "diagnosing ***any*** type of cancer or assessing the tumor burden related to the presence of ***any*** cancer in any organism based solely on the expression level of SEQ ID NO:23702" (emphasis added). Although the Office acknowledges that the application provides "information regarding the relationship between SEQ ID NO:23792 and cancer in Working Example 105" including correlations with breast cancer, colon cancer, and prostate cancer, the Office asserts that the specification does not disclose "that the expression level of SEQ ID NO:23702 is increased in any other types of cancerous cells, such as liver cancer, skin cancer, or lung cancer cells" and "does not teach detection of cancerous cells based solely on the expression of SEQ ID NO:23702". The Office notes that "in the above example [Example 105], the disease status of the patients who contributed tissue was already known ... [and] the working example and specification only describes detection of cancerous cells in human subjects with one of three specific types of cancer."

Applicants disagree with the Office's assertion that the claims lack enablement. Applicants respectfully submit, for example, that the data set forth in the specification show that levels of SEQ ID NO:23702 are significantly upregulated in cancerous cells from a number of different tissues. It would therefore be reasonable to expect levels of SEQ ID NO:23702 to be upregulated in many, if not most or all, types of cancer. Nonetheless, it is believed that this

rejection is met by the amendments to the pending claims. For example, claims 7, 21 and 30, and the claims depending therefrom, were amended to specify that the subject is a human and to specify that the cancer is breast, colon, or prostate cancer.

The Office alleges that "the art teaches that it is entirely unpredictable whether or not the expression level of a particular gene can be used to detect cancerous cells, assess tumor burden, and diagnose cancer" and cites Russo et al. (2003) for the proposition that the "expression level of a single gene is unlikely to function in a diagnostic capacity for any type of cancer" (Office Action, page 9). Applicants, however, do not agree with the Office's characterization of the Russo reference. Russo, for example, does ***not*** state that a single gene cannot function as a diagnostic tool to identify a particular type of cancer. In its summary of microarray-based gene profiling studies for different types of cancer, Russo cites several studies that link single gene expression to specific cancer types. For example, Russo discusses the following studies linking the expression of a ***single*** gene to a particular type of cancer, including:

- Gariboldi et al. (2003), which "suggested a role of the Scaa2 gene...in the genetic predisposition to skin tumors" (Russo, page 6501, col. 1).
- Backert et al. (1999), which found that "studies of colon cancer cells and tissues demonstrated significant suppression of the kinase gene WEE1Hu." (Russo, page 6501, col. 1).
- Five prostate cancer studies which all identified "the transmembrane serine protease hepsin as displaying significantly increased expression in malignant tissues as compared with that of normal prostate tissue" (Russo, page 6499, col. 1).

The Office also cites Russo, alleging that "gene expression results can be unpredictable because false microarray data can be generated from degraded mRNA" (Office Action, page 9). However, Applicants note that this passage appears to have been taken out of context by the Office. Based on a detailed analysis of Russo it is apparent that the authors were instead referring to the general challenges of conducting accurate microarray experiments, and did ***not*** state that gene expression results from scientifically accurate experiments were unpredictable or unreliable (Russo, page 6503, col. 2). The Office's assertion that unpredictability often results from the condition of the human tissue samples used in experiments is similarly taken out of context (Russo, page 6503, col. 2). A detailed analysis of Russo indicates that the authors' comment was again directed at the challenges of obtaining scientifically accurate results from

microarray experiments (Russo, page 6503, col. 2). Furthermore, the comment does not support the Office's contention that the expression level of a single gene cannot be predictably used to diagnose cancer. Even if gene expression results might be "muddled" by mixed tissue samples, Russo does not say that a single gene cannot predictably detect cancerous cells using pure biopsy samples.

The Office further cites the results of Reinholz et al. (2005) in an attempt to illustrate the "unpredictable nature of reliably and reproducibly detecting even a single type of cancer in a human subject based on the observed expression level of a single gene" (Office Action, page 9). Reinholz examined the link between the expression of five genes and the early detection of breast cancer. While the Office discusses that the combined use of the mammaglobin and B305D-C genes has the ***greatest*** observed sensitivity and specificity, Reinholz also reported that the expression of the mammaglobin gene **alone** correctly identified early-stage breast cancer in 72% of the observed cases (Reinholz, page 3729, Table 4). The Office incorrectly appears to reason that because predictability may be ***increased*** by examining the expression of multiple genes, or because the mammaglobin gene did not identify early-stage breast cancer in approximately 20% of patients in the Reinholz study, the presently claimed use of measuring expression of a single gene detect cancer is unpredictable (Office Action, page 10). In contrast, Applicants point out that the correct identification of early-stage breast cancer in a large majority of patients based on the expression of the mammaglobin gene in Reinholz indicates that specific types of cancer can be reliably predicted by the expression of a single gene.

Like almost every other diagnostic test, the presently claimed methods do not identify a cancerous cell 100% of the time. However, the claims do not require this to be the case. For example, the claims do not state that if the gene identified by SEQ ID NO:23702 is not increased, then the cell is not cancerous. Rather, the claims only recite that if the gene identified by SEQ ID NO:23702 exhibits increased expression relative to a control level, such is indicative that the cell is cancerous. More to the point -- satisfaction of the requirements of 35 U.S.C. §112, first paragraph, does not require such. In view of the data set forth in this table, Applicants respectfully submit that one of skill in the art would recognize that expression of a single gene, in this case the gene identified by SEQ ID NO:23702, is indicative of cancer.

Feng et al. (2006) presents a number of potential biomarkers whose expression has been correlated to a variety of different cancer types (Feng, pages 516-521 Table 3). Many of the biomarkers cited are single genes, the expression of which have been shown to detect the presence of specific cancer types with high degrees of sensitivity and specificity. Examples cited in Feng include the RASSF1A, CEA, GRP, and mammaglobin genes for the detection of lung cancer, and the GSTP1, Telomerase, and EPCA genes for the detection of prostate cancer.

The Office alleges that the specification does not teach detection of cancerous cells based solely on the expression of SEQ ID NO: 23702 (Office Action, page 8). However, Applicants point out that Working Example 105 (discussed by the Office) does include experiments that compare the expression profile of SEQ ID NO:23702 in cancerous prostate, colon, and breast cancer cells to normal control cells (present application, page 394). These experiments teach that SEQ ID NO: 23702 is overexpressed in cancerous prostate, colon, and breast cells by at least 2-fold at a 95% confidence level, and can therefore be used to detect these cancer types (present application, pages 399-400; Tables 159-160). It is not relevant that "the disease state of the patients who contributed tissue to the study was already known" (Office Action, page 8) since the purpose of these experiments was to demonstrate correlation between the expression of SEQ ID NO: 23702 and cancerous cells.

The Office argues that the quantity of experimentation required to practice the claimed method of cancer detection is "immense" due to the experimentation required to determine that the increased expression of SEQ ID NO: 23702 can reliably detect specific types of cancer (Office Action, page 11). However, one of the references the Office cites in support of this proposition, Mitas et al. (2001), discusses the use of real-time RT-PCR to validate the clinical utility of gene expression to detect cancer that provides increased sensitivity of detection and decreased sampling error (Mitas, page 162, col. 1) and is "highly automated and rapid" (Mitas, page 163, col. 1). Accordingly, one skilled in the art would understand that any experimentation, if required, would be very amenable to automation. Applicants also remind the Office that in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a

binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where the art typically engages in a complex, but routine degree of experimentation, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*. Even assuming, *arguendo*, that performing experiments to confirm the correlation reported by Applicants between increased expression of SEQ ID NO: 23702 and breast, colon, or prostate cancer is considered "complex" (Applicants respectfully assert that the experimentation is not "complex"), Applicants submit that this kind of experimentation, although complex, is routine in the art, and therefore, is not undue experimentation.

The Office further alleged that the specification and working examples do not teach diagnosing cancer or assessing tumor burden related to the presence of cancer based on the expression of the claimed nucleotide sequence (SEQ ID NO: 23702), because the specification only teaches measuring the expression level of SEQ ID NO: 23702 in human subjects with a known disease status. (Office Action, page 9).

The specification teaches that observation of an increase in the expression level of SEQ ID NO: 23702 is sufficient for detecting the presence of cancer in human subjects. As acknowledged by the Office, Working Example 105 (present application, pages 393-402) presents the results of experiments in which both cancerous and normal human tissues were examined for expression of SEQ ID NO: 23702. These experiments indicated that 17.4% –

26.1% of breast cancer patients and 12.0% – 63.2% of colon cancer patients showed an increased level of SEQ ID NO: 23702 expression (present application, page 399, Office Action, page 8). The experiments also indicated that 1.0% – 3.1% of prostate cancer patients showed an increased level of SEQ ID NO: 23702 expression (present application, page 399, Office Action, page 8).

The Office, however, takes exception to the methodology used in Working Example 105, because both the normal cells and cancerous cells were collected from subjects who had already been diagnosed with cancer (Office Action, page 8). According to the Office, however, measuring the expression of SEQ ID NO: 23702 in human subjects with a known disease status does not enable diagnosing cancer or assessing tumor burden related to the presence of cancer based on the expression of the claimed nucleotide sequence (Office Action, page 9). Applicants do not agree with this assertion.

The specification teaches that the expression of SEQ ID NO: 23702 is increased in cancerous cells ***as compared to normal cells*** (present application, page 394; "a comparison of the gene expression profile of cancerous colon cells (primary tumor) to that of normal colon cells ..."). This is an appropriate methodology for teaching the diagnosis of cancer based on the expression of a nucleotide sequence, because it demonstrates the key discovery that the expression of SEQ ID NO: 23702 is correlated to the presence of breast cancer, colon cancer, and prostate cancer. The disease status of the subjects from which the tissue samples were taken is largely irrelevant to the question of enablement. As discussed above, the claims recite that if the gene identified by SEQ ID NO:23702 exhibits increased expression relative to a control level, such is indicative that the cell is cancerous. The claims do not require a particular source of the control. The known breast, colon and prostate cancer patients' cells served to confirm the usefulness of SEQ ID NO:23702. Additionally, Applicants respectfully ask the Office if its position would be different had the "status" of the cells been determined after assaying for levels of SEQ ID NO:23702. Applicants further ask the Office how one attempting to diagnose cancer could do so without having or understanding at some point in time the characteristics of a known cancerous sample and comparing a test sample against those characteristics.

Evaluating gene expression by comparing expression in cancerous cells to expression in normal cells is an established and valid scientific methodology. In fact, even the scientific publications cited by the Office used this same methodology to link gene expression to cancer

diagnosis. For example, the Russo reference discusses five studies that identified the expression of a single gene which displayed "significantly increased expression in malignant tissues ***as compared with that of normal prostate tissue***" (Russo, page 6499, col. 1; emphasis added). Russo also discusses Martoglio et al. (2000), a study which linked gene expression profiles to ovarian cancer by comparing expression in cancerous tissues to expression in normal ovary tissues (Russo, page 6500, col. 1).

Applicants also note that the results reported in the specification and in Working Example 105 are expressed as a percentage of the total number of subjects in which SEQ ID NO: 23702 was ***over expressed at least two-fold at a 95% confidence interval*** compared to normal cells (present application, page 394). The use of a two-fold difference in expression to define significance suggests that the differences observed represent a legitimate relationship between the expression of SEQ ID NO: 23702 and the presence of breast cancer, colon cancer, and prostate cancer. The high level of correlation between the expression of SEQ ID NO: 23702 and the presence of cancer despite the high threshold for defining a significant relationship provides strong evidence that the expression of SEQ ID NO: 23702 can be used to diagnose cancer and/or assess tumor burden related to the presence of cancer. Comparing gene expression in cancerous cells to expression in normal cells is a valid methodology for teaching the diagnosis of cancer based on the expression of a nucleotide sequence, and indicates that that the expression of SEQ ID NO: 23702 can be used as a diagnostic tool to detect certain types of cancer.

Finally, with respect to the question of whether there is an adequate description of how expression of the subject gene product could be used to measure tumor burden, Applicants respectfully submit that tumor burden may be straightforwardly determined by merely measuring the level of a gene product corresponding to SEQ ID NO:23702. The greater the expression level of the gene product corresponding to SEQ ID NO:23702, the greater the tumor burden. Conversely, the lower the expression level of the gene product corresponding to SEQ ID NO: 23702, the lower the tumor burden. Since Applicants have provided several methods of measuring the expression level of the gene product corresponding to SEQ ID NO:23702, Applicants respectfully submit that a skilled person would be able to measure the tumor burden of a cancer patient using based on the teachings of the present application, without undue experimentation.

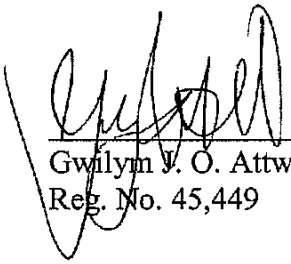
Applicants respectfully submit that the foregoing discussion adequately addresses this aspect of the rejection. In view of the foregoing discussion, withdrawal of this rejection is respectfully requested.

Conclusion

The examination of the pending claims and passage to allowance are respectfully requested. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (302) 778-8458 to clarify any unresolved issues raised by this response.

Please apply any charges or credits to deposit account 06-1050 referencing Attorney Docket No. 20366-130001.

Respectfully submitted,



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